

PCTWORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : B32B 27/08, 27/18, A61J 1/00	A1	(11) International Publication Number: WO 95/16565 (43) International Publication Date: 22 June 1995 (22.06.95)
(21) International Application Number: PCT/IB94/00399 (22) International Filing Date: 8 December 1994 (08.12.94) (30) Priority Data: 3769/93-8 17 December 1993 (17.12.93) CH (71) Applicant (for all designated States except US): BIEFFE MEDITAL S.A. [CH/CH]; Via S. Balestra, 27, CH-6900 Lugano (CH). (72) Inventors; and (75) Inventors/Applicants (for US only): LAMBERT, Philippe [BE/CH]; Serecc da Sora, 7, CH-6926 Montagnola (CH). BUZIO, Pier, Paolo [IT/IT]; Viale Dante, 22, I-28100 Novara (IT). (74) Agent: INCOLLINGO, Italo; Piazzale Lavater 3, I-20129 Milano (IT).		(81) Designated States: AU, BR, CA, CN, JP, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
(54) Title: MULTILAYER COEXTRUDED FILM FOR PARENTERAL SOLUTIONS BAGS (57) Abstract A cast-coextruded film for sterilizable, low extractable containers of parenteral solutions, which is flexible, transparent, heat-sealable, free from aromatic adhesive, incinerable without fumes, consists at least of: a layer of polyamide, a layer essentially of LLDPE, and a polymeric adhesive layer of ethylene polymer or copolymer.		

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	GB	United Kingdom	MR	Mauritania
AU	Australia	GE	Georgia	MW	Malawi
BB	Barbados	GN	Guinea	NE	Niger
BE	Belgium	GR	Greece	NL	Netherlands
BF	Burkina Faso	HU	Hungary	NO	Norway
BG	Bulgaria	IE	Ireland	NZ	New Zealand
BJ	Benin	IT	Italy	PL	Poland
BR	Brazil	JP	Japan	PT	Portugal
BY	Belarus	KE	Kenya	RO	Romania
CA	Canada	KG	Kyrgyzstan	RU	Russian Federation
CF	Central African Republic	KP	Democratic People's Republic of Korea	SD	Sudan
CG	Congo	KR	Republic of Korea	SE	Sweden
CH	Switzerland	KZ	Kazakhstan	SI	Slovenia
CI	Côte d'Ivoire	LI	Liechtenstein	SK	Slovakia
CM	Cameroon	LK	Sri Lanka	SN	Senegal
CN	China	LU	Luxembourg	TD	Chad
CS	Czechoslovakia	LV	Latvia	TG	Togo
CZ	Czech Republic	MC	Monaco	TJ	Tajikistan
DE	Germany	MD	Republic of Moldova	TT	Trinidad and Tobago
DK	Denmark	MG	Madagascar	UA	Ukraine
ES	Spain	ML	Mali	US	United States of America
FI	Finland	MN	Mongolia	UZ	Uzbekistan
FR	France			VN	Viet Nam
GA	Gabon				

Title: Multilayer coextruded film for parenteral solutions bags.

DESCRIPTION

The present invention concern flexible, transparent multilayer coextruded films, on one layer of which can be possibly laminated further layers. More particularly the invention concerns a coextruded multilayer film for sterilizable, low extractable containers of parenteral solutions, said film being; flexible and transparent before and after steam sterilization, heatseable to itself and/or to the parenteral solution container access ports by its inner or outer layer; free from aromatic adhesive, incinerable without release of halogen containing fumes; and comprising at least a layer of olefin (co-) polymers and a layer of amide (co-) polymer.

The wide diffusion of plastic containes (bags, pouches) for parenteral solutions is known; consequently also the requirement of having films adequate to this purpose is known.

PRIOR ART

The Prior Art has suggested a lot of flexible films comprising layers of polyamide (PA) and of polyethylene (PE), all certainly interesting however not free of inconveniences. In particular US Patent N° 4,326,574 describes flexible bags made of laminates consisting of an outer layer of polypropylene (PP), an inner layer of polyethylene (PE) (in this case a polymer sustantially of ethylene units combined with a minor proportion of butylene units), and of a central layer of polyamide (PA).

The film is obtained by lamination with the aid of a polyurethane adhesive which can, in case, decompose and/or migrate into the solution

during and after steam sterilization. All attempts to reproduce such a structure by coextrusion failed: the blown coextruded PP-PA-PE had unacceptable transparency whereas the cast coextrudates could be obtained only with a PE-copolymer of very low molecular weight which was however not sterilizable in autoclave. European Patents N° 15775 and II° 102738, and US Patents N° 3,791,915 and N° 3397382 describe several solutions which for one or the other reason do not appear to have had the hoped success.

It has now been found (not without surprise) that the inconveniences present in the Prior Art, either in the phase of the film coextrusion or in the phase of form-and filling and sterilization of the bags, are eliminated with the coextruded film according to the invention which are characterized by at least three layers:

- A) an outer layer having a thickness of from 10-60 preferably 15 to 50 microns and consisting of one or more polyamides (PA);
 - B) an inner layer having a thickness of from 60 to 150 preferably from 80 to 130 microns, consisting of a linear low density (co-) polymer of ethylene (LLDPE) with a minor proportion from 0,5 to 10% of an alfa-olefin containing from 4 to 12 carbon atoms, or of a blend of this (co-) polymer with from 5 to 25% of a low density polyethylene (LDPE), and containing from 0,1 -3% of a slip agent;
 - C) a polymer adhesive intermediate layer having a thickness of from 3 to 20 microns and consisting of polyethylene (s) or ethylene copolymers with vinyl acetate (EVA), grafted with from 0,1 to 0,7% of maleic anhydride.
- In one embodiment particularly advantageous, two further layers D) and E) are provided by coextrusion on the polyamidic layer A), the layer D)

with a thickness of from 3 to 5 microns consisting of polyethylene or polypropylene treated with maleic anhydride and the layer E) with a thickness of from 20 to 60 microns consisting of a statistic (co-) polymer of propylene or of polyethylene. In an other embodiment the layer D) is laminated on the polyamide layer with a polyurethanic adhesive layer with a thickness of from 2 to 10 micron.

From these fully coextruded or coextruded-laminated films according to the invention, pouches were prepared showing high characteristics of seal strength, softness, transparency, weldability and tensile strength. Characteristically the adhesive resin between the polyamide (PA) layer A) and the polyethylene (PE) layer B) is preferably selected from the group of polyethylene (s) (LLDPE or LPDE) containing 0,1 - 0,7% of maleic anhydride (AM) whereas the resin between the layers A) (PA) and E) (PP) is polypropylene with 0,1 - 0,5% maleic anhydride.

For bags up to three liters of parenteral solution the preferred thickness and composition of the film according to the invention are as follows:

layer	composition	thickness, micron	preferred thickness
A	PA	10-50	15-35
B	PE	60-150	80-130
C	LDPE or LLDPE 0,1-0,7% AM	5-20	7 -15
adhesives or			
D	PP 0,1-0,5% AM	3-20	7-15
E	PP	20-100	15-40

The further features and advantages of the invention will better appear from the examples describing the embodiments schematically represented in the drawing in which Figure 3 shows an open pouch SA sealed on the edges LA and provided with a valve VA, Figure 1 shows the basic coextrudate with three layers A) (PA), B) (PE) and C) (adhesive) formed of polyethylene PE grafted with maleic anhydride (AM): and Figure 2 shows the relevant coextrudated/laminated of 5 layers i. e. with the addition of layers D') (adhesive = Polyurethane, PU) and E) (PP): and Figure 2a shows the fully coextrudated 5 layers film formed of the basic 3 layers (A-C-B) structure of Fig. 1, and of the additional two coextruded layers D) and E) consisting respectively of maleic anhydride grafted polypropylene (PP.AM), and of polypropylene (PP).

Description of the preferred embodiments

The examples 1 - 6 below illustrate the preferred (but not limitative) embodiments.

Ranges of thickness (in microns) for containers up to 3 liters

A	(PA)	10-5
B	(PE)	60-150
C	(Polymeric adhesive)	5-20
D	(Polymeric adhesive)	5-20
E	(PP)	10-50

Example 1

A multilayer structure (ABC) containing 3 layers (Fig. 1):

The outer layer (A) consists of 30 microns polyamide-6 from EMS (grade XE 3314); the inner layer (B) consists of 110 microns of C₈-LLDPE from DSM (grade Stamylex 1046) additivated with 500 ppm of Erucamide slip agent (1% masterbatch Polybatch slip FSU 105 E of Schulman); the adhesive layer (C) consists of 10 microns of a 1 : 1 blend of 2 low density polyethylenes (LDPE) grafted with about 1.8% maleic anhydride such as those of DUPONT Bynel 402 and 408.

This coextruded structure was used to fabricate one liter pouches on a form-fill-seal (FFS) machine at 25 bags/minute; which were sterilized at 118°C. exhibited low extractables, good transparency and were leak free.

The same structure was also gravure printed on the polyamide (PA) side (A) and then was laminated with a cast film consisting of random propylene-ethylene copolymer such as MOPLEN EP1X35F of HIMONT having a thickness of 50 microns (layer E); the adhesive layer (D¹) between the coextruded structure (A-B-C) and layer (E¹) was a conventional two components polyurethane glue with a coating weight dry matter of 3 gr./m². The resulting semi-coextrudate/laminate film (Fig. 2) was processed through the same FFS machine to obtain leak free parenteral containers that exhibited excellent transparency and low extractables.

Film processing conditions

The above structure A B C was produced on a REIFENHÄUSER COMPACT cast coextrusion line for multilayer sheet film.

Line output:	200 kg/hour
Chill roll temperature:	38°C - 40°C on PA side
Winding speed:	13.5 m/min.
Air knife combined with air suction under the die.	
Feedblock:	265°C
Die:	1.5 meter wide - 272° to 274°C
• PA extruder	
screw diameter:	70 mm
output:	55 kg/hr.
RPM:	28
Barrel temperature:	245 to 260°C
Filter:	260°C

- PE extruder
 - screw diameter: 90 mm
 - output: 120 kg/hr.
 - RPM: 40
 - Barrel temperature: 165 to 210°C
 - Filter temperature: 200°C
- Polymeric adhesive extruder:
 - screw diameter: 50 mm
 - output: 15 kg/hr.
 - RPM: 40
 - Barrel temperature: 165°C to 210°C
 - Filter temperature: 200°C

Table 1: semi-coex and semi-coex laminate properties (Example 1)

Film properties	(a)	(b)	(c)
Total thickness (microns)	200	200	148
Interlayer adhesive strength			
PA/PE (N/15 mm)	12.0	7.5	11.0
PA/PP (N/15 mm)	11.0	6.0	---
Seal strength (N/15 mm)			
PE/PE	75	70	55
PP/PP	35	30	---
Tensile strength (MPa)			
MD/TD	38/30.5	30.7/27.8	29/25.8
Yield strength (MPa)			
MD/TD	19.3/19	24.5/23.9	18.9/18.8
Elongation at break %			
MD/TD	526/481	407/435	421/407
1% secant modulus (MPa)			
MD/TD	136/137	110/116	120/116
Coefficient of friction (COF) - static			
PE/PE	0.30	0.26	0.32

- Note:**
- (a) semi-coex / laminate before sterilization
 - (b) semi-coex / laminate after sterilization
 - (c) semi-coex / before lamination after sterilization

Example 2

A 3 layers structure consisting of:

The outer layer (A) consists of 30 microns of a 20/80 blend of copolyamide PA_{6/12} - PA₆ of respective grades EMS XE 3303 and EMS XE 3180. (*)

The inner layer (B) consists of 100 microns of C₈-LLDPE - DOWLEX SC 2100 additivated with 500 ppm slip agent (1% masterbatch FSU 105 E of Schulman). (**)

The adhesive layer (C) consists of 10 microns of grafted LLDPE YPAREX 8104E from DSM. (*) C₈-LLDPE indicates linear low density polyethylene containing octene; (**) E means Erucamide.

The processing conditions and film properties are comparable to those of the structure (c) of Example 1

Example 3

A 3 layers structure consisting of:

The outer layer (A) consists of 30 microns of polyamide-6 from EMS - grade XE 3180

The inner layer (B) consists of 110 microns of a 80/20 blend of C₈ LLDPE from DSM (grade Stamylex 1026) and LDPE from Exxon (grade Escoreme LD 100 AG) additivated with 500 ppm slip agent (1% masterbatch FSU 105 E = Erucamide)

The adhesive layer (C) consists of 10 microns of maleic anhydride grafted LLDPE from MITSUI (grade ADMER NF 530 E).

The processing conditions and film properties are similar to those of the structure (c) of Example 1.

Example 4

A fully coextruded 5 layers film (figure 2a)

A five layers structure(EDACB) consisting of a core layer (A) consisting of 30 microns of polyamide₆ from EMS (grade XE 3180); an inner layer (B) consisting of 100 microns of C₈ LLDPE from DSM (grade Stamylex 1026) additivated with 500 ppm Erucamide slip agent (1% masterbatch Polybatch slip FSU 105 E of Schulman); a polymeric adhesive layer (C) between layer (A) and (B), consisting of 8 microns of maleic anhydride grafted LLDPE YPAREX 8104 E from DSM; an outer layer (E) of 35 microns of ethylene-propylene random copolymer from PCD - DAPLEN KFC 2206SB; a polymeric adhesive layer (D) consisting of 10 microns of maleic anhydride grafted polypropylene (PP) from ATO (grade OREVAC PP-FT), between layers (A) and (E).

Film processing conditions

The line on which the structure was produced is the same as on Example 1.

Total output: 200 kg/hour
 Chill roll temperature: 38°C - 40°C on the LLDPE side
 Winding speed: 13.5 m/min.
 Air knife combined with air suction under the die.
 Feedblock temperature: 265°C
 Die: 1.5 meter wide - 271°C to 274°C

- PA extruder
 - screw diameter: 50 mm
 - output: 35 kg/hr.
 - RPM: 55
 - Barrel temperature: 235°C to 250°C
 - Filter: 248°C
- PP extruder
 - screw diameter: 90 mm
 - output: 35 kg/hr.
 - RPM: 20
 - Barrel temperature: 210°C to 242°C
 - Filter temperature: 240°C
- LLDPE extruder
 - screw diameter: 70 mm
 - output: 110 kg/hr.
 - RPM: 70
 - Barrel temperature: 200°C to 240°C
 - Filter temperature: 250°C
- PP adhesive extruder
 - screw diameter: 50 mm
 - output: 10 kg/hr.
 - RPM: 38
 - Barrel temperature: 190°C to 220°C
 - Filter temperature: 220°C
- PE adhesive extruder
 - screw diameter: 50 mm
 - output: 10 kg/hr.
 - RPM: 27
 - Barrel temperature: 190°C to 225°C
 - Filter temperature: 230°C

Table 2: 5 layers coextrudate properties (Example 4)

Film properties before sterilization	Values
Total thickness (microns)	185
Interlayer adhesive strength (N/15 mm)	
PA/PE	17
PA/PP	15
Seal strength (N/15 mm)	
PE/PE	70
PP/PP	33
Tensile strength (MPa)	
MD/TD	34.6/26.8
Yield strength (MPa)	
MD/TD	15.3/15.0
Elongation at break %	
MD/TD	490/430
1% secant modules (MPa)	
MD/TD	125/118
Coefficient of friction (COF) - static	0.32

Example 5

A fully coextruded 5 layers film

A five layer structure (E D A C B) consisting of the same composition and thickness as in example 4 with the exception of layer A, which contains a modified PA consisting of a blend of 85% of polyamide-6 from EMS grade XE 3180 and 15% of PA 6I/6T from EMS grade Grivory G21.

Film processing conditions

Same as Example 4 with the exception of PA extruder (A).

- PA extruder (A) screw diameter: 50 mm
 output: 35 kg/hr.
 RPM: 56
 Barrel temperature: 235°C to 248°C
 Filter temperature: 248°C.

Table 3: 5 layers coextrudate properties (Example 5)

Film properties before sterilization	Values
Total thickness (microns)	183
Interlayer adhesive strength (N/15 mm)	
PA/PE	20
PA/PP	16
Seal strength (N/15 mm)	
PE/PE	85
PP/PP	35
Tensile strength (MPa)	
MD/TD	36/34
Yield strength (MPa)	
MD/TD	14.5/14.8
Elongation at break %	
MD/TD	480/500
1% secant modulus (MPa)	
MD/TD	132/130
Coefficient of friction (COF) - static	0.34

Example 6

A 3 layers structure was prepared as follows:

The outer layer (A) consists of 30 microns of a blend of 85% polyamide₆ from EMS, grade XE 3180 and 15% of polyamide 6I/6T from EMS, grade Grivory G21.

The inner layer (B) consists of 110 microns of C₈ LLDPE from DSM (Grade Stamylex 1026) additivated with 500 ppm Erucamide slip agent (1% masterbatch Polybatch slip FSU 105E).

The adhesive layer (C) consists of 10 microns of maleic anhydride grafted LLDPE YPAREX 8104 E from DSM.

Film processing conditions

The line on which the structure was produced is the same as on Example 1; also the same processing conditions apply with the exception of ¹⁾ the polyamide extruder (C).

- Polyamide extruder (C) screw diameter: 70 mm
 output: 60 kg/hr.
 RPM: 30
 Barrel temperature: 235°C to 255°C
 Filter temperature: 255°C.

²⁾ The die temperature is between 270° and 273°C.

Table 4 : semi coextrudate properties (Example 6)

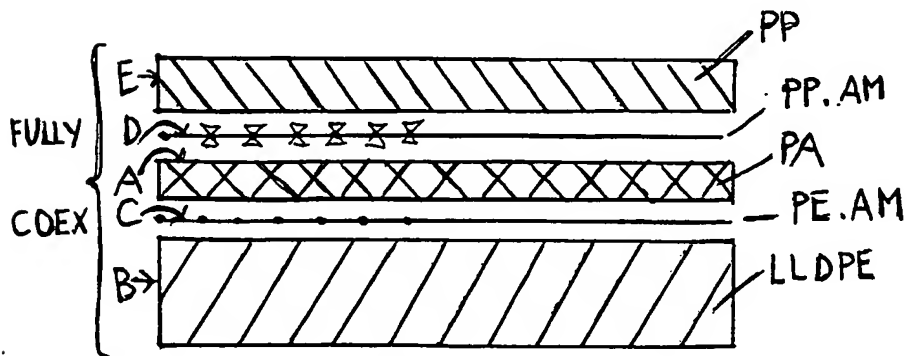
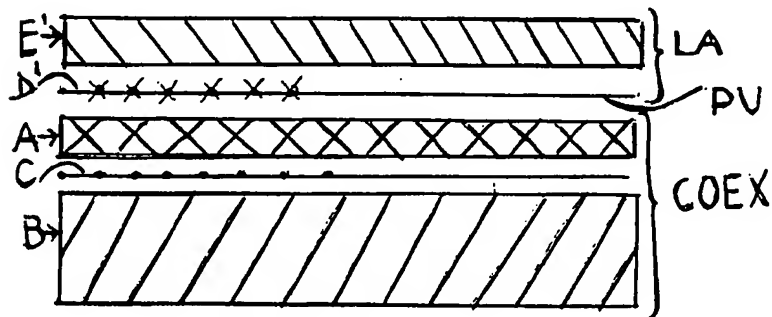
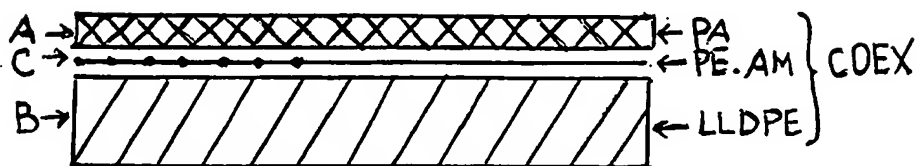
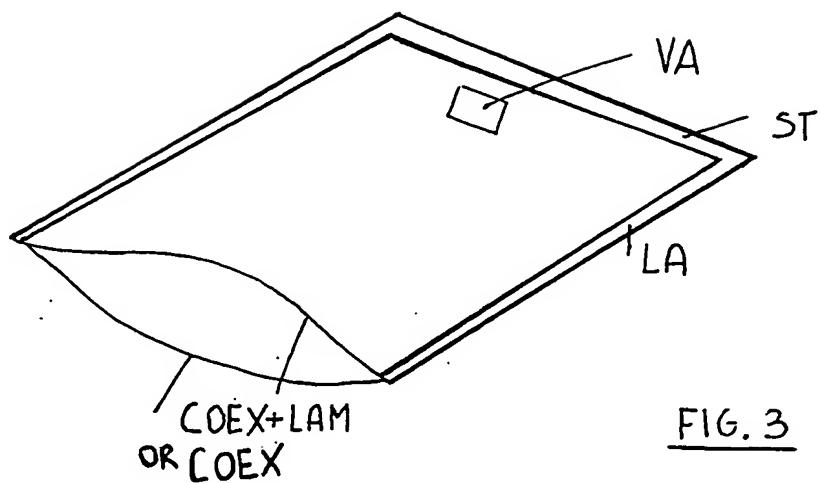
Film properties before sterilization	Values
Total thickness (microns)	148
Interlayer adhesive strength (N/15 mm) PA/PE	19
Seal strength (N/15 mm) PE/PE	72
Tensile strength (MPa) MD/TD	31/29.5
Yield strength (MPa) MD/TD	19/18
Elongation at break % MD/TD	480/505
1% secant modulus (MPa) MD/TD	132/124
Coefficient of friction (PE/PE) (COF) - static	0.32

CLAIMS

- 1) Cast-Coextruded multilayer film for sterilizable, low extractable containers of parenteral solutions, said film being: flexible and transparent before and after steam sterilization, heatsealable to itself and/or to the parenteral solution container access ports, by its inner or outer layer; free from aromatic adhesives; incinerable without release of halogen containing fumes; and comprising at least a layer of olefin (co-) polymers and a layer of amide (co-) polymer, characterized in that the film is made up of at least:
 - A) an outer layer having a thickness of from 10-60 preferably 15 to 50 microns and consisting of one or more polyamides (PA);
 - B) an inner layer having a thickness of from 60 to 150 preferably from 80 to 130 microns, consisting of a linear low density (co-) polymer of ethylene (LLPDE) with a minor proportion from 0,5 to 10% of an alfa-olefin containing from 4 to 12 carbon atoms, or of a blend of this (co-) polymer with from 5 to 25% of a low density polyethylene (LDPE), and containing from 0,1 - 3% of a slip agent;
 - C) a polymeric adhesive intermediate layer having a thickness of from 3 to 20 microns and consisting of polyethylene (s) or ethylene copolymer with vinyl acetate (EVA), grafted with from 0,1 to 0,7% of maleic anhydride.
- 2) Coextruded multilayer film according to claim 1, characterized by two further layers (D) and (E) coextruded on the polyamide layer (PA), layer (D) having thickness of from 3 to 15 microns and consisting of low density polyethylene or polypropylene grafted with maleic anhydride, and

layer E) having a thickness of 20 to 100 microns and consisting of a random propylene copolymer with a diene, or of polyethylene.

- 3) Coextruded film according to claim 1, characterized by a further layer (E') which consists of polyethylene or polypropylene, has a thickness of from 20 to 100 microns and is laminated on the polyamide layer (PA) with a polyurethane adhesive layer (D') having a thickness of from 2 to 10 micron.
- 4) Bags in particular pouches formed of films according to the above claims, said pouches containing parenteral solutions, and being flexibles and transparent before and after sterilization.



INTERNATIONAL SEARCH REPORT

International Application No

PCT/IB 94/00399

A. CLASSIFICATION OF SUBJECT MATTER
 IPC 6 B32B27/08 B32B27/18 A61J1/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 B32B A61J

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO,A,86 02041 (FUJIMORI KOGYO CO., LTD.) 10 April 1986 see page 4, line 33 - page 5, line 5; claims see page 5, line 29 - page 6, line 2 see page 8, line 32 - line 34 see page 9, line 17 - line 32 ---	1-4
Y	EP,A,0 183 512 (AMERICAN CAN COMPANY) 4 June 1986 see page 1, line 1 - line 13; figure 3 see page 12, line 1 - line 17 see page 18, line 3 - page 19, line 3 --- -/--	1-4

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
 "E" earlier document but published on or after the international filing date
 "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
 "O" document referring to an oral disclosure, use, exhibition or other means
 "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
 "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
 "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
 "&" document member of the same patent family

Date of the actual completion of the international search

24 March 1995

Date of mailing of the international search report

10.04.95

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
 NL - 2280 HV Rijswijk
 Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
 Fax (+31-70) 340-3016

Authorized officer

Pamies Oille, S

INTERNATIONAL SEARCH REPORT

Intern. Application No
PCT/IB 94/00399

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,A	DATABASE WPI Week 9432, Derwent Publications Ltd., London, GB; AN 94-260057 (32) & JP,A,6 190 990 (OTSUKA SEIYAKU KOGYO KK) 12 July 1994 see abstract ---	1-4
A	US,A,4 687 688 (CURIE ET AL.) 18 August 1987 see column 1, line 51 - column 2, line 2; figure 1 see column 3, line 42 - line 59 ---	1
A	EP,A,0 506 348 (W.R. GRACE & CO.) 30 September 1992 see page 4, line 14 - line 24; claims see page 5, line 44 -----	1,2,4

INTERNATIONAL SEARCH REPORT

Intern. Application No.

PCT/IB 94/00399

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A-8602041	10-04-86	US-A- 4686125	11-08-87
		AU-B- 579894	15-12-88
		AU-A- 4778085	17-04-86
		CA-A- 1266425	06-03-90
		EP-A, B 0197951	22-10-86
		JP-T- 62502112	20-08-87

EP-A-0183512	04-06-86	US-A- 4640852	03-02-87
		JP-A- 61179737	12-08-86
		SE-A- 8505546	29-05-86
		US-A- 5154789	13-10-92
		US-A- 4818592	04-04-89

US-A-4687688	18-08-87	US-A- 4767651	30-08-88
		US-A- 4862675	05-09-89

EP-A-0506348	30-09-92	NONE	
